UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

ROCHE DIAGNOSTICS GMBH and ROCHE MOLECULAR SYSTEMS, INC., Plaintiffs and Counterclaim Defendants, v. ENZO BIOCHEM, INC. and ENZO LIFE SCIENCES, INC. Defendants and Counterclaim Plaintiffs.	)	04 CV 4046 (RJS)

DECLARATION OF DR. DAVID H. SHERMAN

I. INTRODUCTION

1. I submit this declaration in this case on behalf of Enzo Biochem, Inc. and Enzo Life Sciences, Inc. (collectively, "Enzo") on claim construction issues relating to U.S. Patent Nos. 4,943,523 ("the '523 patent") and 5,082,830 ("the '830 patent").

2. I have been retained by Greenberg Traurig, LLP as an expert in this case. I am being compensated at my usual rate of $600 per hour for work on this case. None of my compensation is dependent upon the outcome of this case.

II. QUALIFICATIONS

3. A copy of my curriculum vitae is attached as **Exhibit A** to this declaration.

4. I am the Hans W. Vahlteich Professor of Medicinal Chemistry and a Professor of Microbiology and Immunology, Chemistry, and Research in the Life Sciences Institute at the University of Michigan (UM), where I serve as the Director of the Center for Chemical Genomics. I am also currently the Associate Dean for Research and Graduate Education at the

UM College of Pharmacy. I have been a professor at the University of Michigan since 2003. Prior to that time, I spent almost 15 years as a Professor of Microbiology and Biotechnology and as Director of the Center for Microbial Physiology and Metabolic Engineering at the University of Minnesota. During the course of my career, I have taught many undergraduate and graduate level courses in microbiology, medicinal chemistry, and chemical biology (including synthetic, and biochemical approaches to drug discovery).

5. I earned a Bachelor of Arts in Chemistry with Honors from the University of California at Santa Cruz in 1978, and a Ph.D. in Organic Chemistry from Columbia University in 1981. After graduating, I conducted postdoctoral research in the Department of Pharmacology at Yale University from 1981 to 1982, and at the Center for Cancer Research at the Massachusetts Institute of Technology (M.I.T.) from 1982 to 1984. While at M.I.T., I performed research in molecular immunology with Dr. Herman Eisen relating to development of antibodies against labels, dyes, chemical groups and other epitopes.

6. I have substantial experience developing diagnostic and immunodiagnostic products, having held the position of research scientist at Biogen Research Corporation from 1984-1987 and at the John Innes Institute from 1987-1990. I have continuously served as a technical consultant advising on issues relating broadly to drug discovery since 1991 for well-known biotechnology and pharmaceutical industry leaders such as Merck, Wyeth Research, and Pfizer, Inc. among others.

7. As part of my research relating to drug discovery and small molecule synthesis and in connection with my consulting work, I have synthesized nucleic acid probes and small molecules, and developed and employed several types of biotinylated molecules.

8. I have authored or co-authored more than 200 publications, of which more than 10 concern my research on chelators that bind metals to become part of a complex. I have also

authored a chapter in the Manual of Industrial Microbiology and Biotechnology dealing with microbial production of small molecules, and a chapter in the book Aziridines and Epoxides in Organic Synthesis concerning the introduction of hydroxyl group functionality using biological and chemical methods. In addition, I have lectured extensively at more than 100 industry and academic conferences on topics such as chemistry, biochemistry, biopolymers, medicinal chemistry, molecular biology and related subjects. I am the named inventor of nine patents, including two relating to various nucleic acid and polypeptide technologies.

9. I serve as a referee of research articles submitted to several prestigious peer-reviewed journals including among others, Tetrahedron, Nature, Science, Journal of the American Chemical Society, Organic Letters, Molecular Microbiology, Chemistry & Biology, Nature Chemical Biology, Nature Chemistry, and Biotechnology Progress.

10. During my career, I have received several awards and recognition for my work as a medicinal and organic chemist. For three consecutive years from 1990 to 1992, I was honored with the Eli Lilly Life Sciences Award for my work on the biotechnology of drug discovery and development. In 2008, I was elected a Fellow of the American Association for the Advancement of Science. In 2009, I received both the A.C. Cope Scholar Award from the American Chemical Society for excellence in organic chemistry, and the Charles Thom Award from the Society for Industrial Microbiology for outstanding research contributions in biotechnology.

III. MATERIALS CONSIDERED

11. In forming my opinions, I have relied upon my knowledge of the state of the art at the time of the invention (e.g., in or before 1984 with respect to the ‘523 patent and 1986 with respect to the ‘830 patent). Additionally, I have reviewed the ‘523 and ‘830 patents. (Exs. 1 and

2)[1], their file histories (Exs. 4 and 5), related patents and file histories, the parties' Joint Claim Construction and Prehearing Statement (Ex. 3), relevant scientific publications and textbooks, various documents produced and/or served by the parties in this case, and other publicly available information. A list of materials I reviewed in connection with this declaration is attached as **Exhibit B** to this declaration.

12. I have been informed that the parties in this case have agreed that for purposes of these patent infringement proceedings, the Court's prior claim construction of the claim terms "A^3—(X—R^1—E—Det^b)$_m$" and "—X— is selected from the group consisting of [listed structures]" of U.S. Patent No. 4,707,440 in *Enzo Biochem, Inc., et al. v. Amersham PLC et al.,* 439 F. Supp. 2d 309, 319-21 (S.D.N.Y. 2006), shall apply to like claim terms and phrases of the '523 patent, including the following constructions relevant to this declaration:

- The chemical groups provided for as "X" are oriented as pictured in the claims, with the left-most element attached to "A^3" and the right-most element attached to "R^1";
- The bonds between the components in the "descriptive" or "modular" formula "A^3—(X—R^1—E—Det^b)$_m$" allow for covalent as well as for non-covalent bonds; and
- "A^3—(X—R^1—E—Det^b)$_m$" does not contain intervening structures.

I have therefore considered this prior claim construction in forming my opinions with respect to the '523 patent.

13. I have also been informed that the parties in this case have further agreed that the Federal Circuit's claim construction of the '830 patent, as affirmed in *Enzo Biochem, Inc. v.*

[1] All numbered exhibits cited in this declaration are exhibits to the Declaration of Justin A. Maclean submitted concurrently with Enzo's Opening *Markman* Brief Related to U.S. Patent Nos. 4,943,523 and 5,082,830.

Applera Corp., 539 F.3d 1325, 1340-43 (Fed. Cir. 2010), should be adopted by the Court. Thus, I have considered this construction and related findings in forming my opinions with respect to the '830 patent, including the following:

- The term "non-radioactive moiety" means "a moiety that is utilized in indirect detection, i.e., a moiety that can be detected with a preformed detectable molecular complex"; and
- There is "no requirement that a preformed detectable molecular complex be actually present in claim 1; rather, it simply requires the 'non-radioactive moiety' to be capable of performing a function: "*can* be detected with a preformed detectable molecular complex.'"

I reserve the right to amend and/or supplement my opinions to the extent that the Court does not adopt the Federal Circuit's claim construction.

IV. LEGAL BASIS FOR OPINION

14. I understand that claim construction is an issue of law for the Court.

15. I am informed that the words of a claim are generally given their ordinary and customary meaning that they would have to a person of ordinary skill in the art at the time of the invention (POSA). To determine the meaning of a claim term, I am informed that the Court will look first to the claims and specification, then to the file history, and only if necessary, to other extrinsic evidence. After being informed of any relevant applicable legal principles, I provide my opinion herein as to the meaning of certain claim terms to POSA, to the extent they may be useful to the Court in understanding the technical aspects of the patents and determining the meaning of specific terms.

V. OPINION CONCERNING THE '523 PATENT

A. Background

16. The '523 patent issued on July 24, 1990 from Application No. 43,670 filed on April 28, 1987, which was a divisional application of earlier filed Application No. 575,396 from which Enzo's U.S. Patent No. 4,707,440 issued. The '523 patent expired on July 24, 2007. (Ex. 1.)

17. The '523 patent is directed to detectable molecules of the general formula A^3—$(X—R^1—E—Det^b)_m$, and methods of using those detectable molecules to detect other compounds in a biological sample, including for example, compounds such as hormones, proteins, small molecules, drugs, antigens, or nucleic acid sequences. (*See*, *e.g.*, Ex. 1 at 20:7-21:29.)[2] The patent provides examples of methods of chemically synthesizing the detectable molecules. (Ex. 1 at 12:18-20-5.) In general, the detectable molecules have a polymer (which may be a biopolymer) or low molecular weight molecule, that is attached to a detectable agent (e.g., a biotin-containing group, metal chelator, a compound capable of yielding a metal chelator) *via* a chemical linker, without interfering with the signaling ability of the detectable agent or the stability of the detectable molecule as a whole. (*See*, *e.g.*, Ex. 1 at 1:9-13; 3:20-65.) The '523 patent refers to the biopolymer or low molecular weight molecule as "A^3." (*See*, *e.g.*, Ex. 1 at 4:1-11; Claim 1.) The patent discloses that A^3 may be modified so that it is capable of attachment to the portion of the molecule comprising "X—R^1—E" where each one of "X," "R^1," and "E" are different groups comprising listed chemical structures. (*See*, *e.g.*, Ex. 1 at 6:9-57; 9-10 (Table 1); 15:38-16:54; 33:21-51 (Example 16); Claim 1.) At the other end of the compound, "E" is attached to "Det^b" which can be a biotin-containing group, metal chelator, a compound capable of yielding a metal chelator. (*See*, *e.g.*, Ex. 1 at 9-10 (Table 1); 16:67-17:3 and Scheme VI.)

[2] Throughout this declaration, citations to the relevant column and line numbers of the patents are identified with the following format: "column number: line number".

18. The disclosed and claimed detectable molecules and methods are capable of use in an "unlimited" number of applications including for example, sandwich and competitive immunoassays, diagnosis of genetic disorders, detection of nucleic acid sequences, and imaging (including with monoclonal antibodies). (*See*, *e.g.*, Ex. 1 at 5:1-18; 20:8-21:28.)

B. Person of Ordinary Skill in the Art

19. It is my opinion based on the materials I have reviewed and my own knowledge of the state of the art during the relevant time frame of the '523 patent, that a POSA at the time of '523 invention would have been a person in the field of chemistry who possesses or could have been actively pursuing an advanced degree in chemistry (i.e., Masters or above) who has done course work in life sciences (e.g., molecular biology, biochemistry).

C. Claim Construction of Disputed Claim Terms

1. "at least one modifiable reactive group"/ "modified reactive groups"/"reactive group"

20. I understand that Roche does not propose a meaning for the phrases "at least one modifiable reactive group" and "modified reactive groups" (or any of the chemical groups to which they refer), but instead argues that those phrases are indefinite or incapable of being understood by a POSA. I disagree.

21. In my view, after reviewing the claims and specification of the '523 patent as well as other materials, the claim phrases "at least one modifiable reactive group" and "modified reactive groups" are not only definite, but a POSA would have readily understood them to refer to the one or more reactive chemical groups which are modifiable and become part of A^3 so as to give a modified A^3 that can attach to X.

22. The intrinsic evidence of the '523 patent fully supports my opinion. Claim 1 expressly states that A^3 must have at least one modifiable reactive group "consisting of amino,

hydroxyl, 1, 2-cis diOH, halide aryl, imidazoyl, carbonyl, carboxyl, thiol or a residue comprising an activated carbon." (Ex. 1 at 37: 63-66 (emphasis added); *see also* 6:27-52.) The structure of each of the nine chemical groups in this claimed list would have been well known at the time to a POSA, including for use in attaching chemical structures such as those described in the claim. That clear purpose of the modifiable reactive group is described and confirmed by the '523 patent specification and file history. (Ex. 1 at 7:34-36; Ex. 4 (9/15/89 Response) at 8 ("The purpose of this reactive group is to bond with an —X— moiety. . . .")

23. In my opinion, a POSA would further understand from the clear statements in the '523 specification that the modifiable reactive group could either be present on A^3 or else introduced *via* known chemical methods onto A^3, so A^3 has a way to attach to X. (*See*, *e.g.*, Ex. 1 at 6:24-26 ("it is necessary that the entity A^3 …prior to reaction have at least one and up to several modifiable reactive groups"); 6:53-55; 9-10 (Table 1); 15:38-16:54; 33:21-51 (Example 16); Claim 1; and 6:9-57 generally.) The patent provides a simple schematic of an A^3 with a modifiable reactive group that is further modified so that A^3 can attach to X. (Ex. 1 at 15 (Scheme V).) Therefore, consistent with the patent, a POSA would readily understand the counterpart claim phrase "modified reactive groups" to mean one or more reactive chemical groups which are modified as part of a modified A^3 when A^3 is attached to X.

24. Thus, in my opinion, a POSA would also understand that when the claimed modifiable reactive groups are used to attach chemical structures, they necessarily become "modified," and, that basic concept is what is being claimed. (Ex. 1 at 6:24-26.)

25. There is nothing in the '523 file history that contradicts my conclusion that a POSA would have readily understood this clearly defined meaning and scope of the "modifiable reactive groups" and that those modifiable reactive groups become "modified" in the final compound as claimed. For this reason, it is also my view that the term "at least one modifiable

reactive group" is wholly consistent with and makes perfect sense with the later claimed "modified reactive groups."

26. While I generally agree with Roche's position that the claim term "reactive group" can be construed, their argument that the terms "modifiable" and "modified" cannot be understood by a POSA is not plausible. For the same reasons stated above, I believe a POSA would readily understand the term "reactive group" from the plain language of the claim to mean and refer to the specified list of chemical groups "amino, hydroxyl, 1, 2-cis diOH, halide aryl, imidazoyl, carbonyl, carboxyl, thiol or a residue comprising an activated carbon."

27. In my opinion, Roche's proposed construction is at odds with the '523 patent claims and specification. Claim 1 is directed to a detectable molecule. Nothing in the claim or the patent specification imposes requirements as to how that detectable molecule is synthesized. Roche improperly limits the "detectable molecule" of the claims by adding requirements of functionality, a sequence of reactions including undergoing "a reaction to bond," and the formation of detectable molecule, which steps are neither appropriate nor required by the composition of matter that is claimed.

2. "a residue comprising activated carbon"

28. Roche's construction of this term is similarly flawed in that it seeks to add a number of limitations, such as "a monomer that is present in a polymer," the nature of the carbon atom, and synthetic methods including the nature of the reactions and the compound it is capable of reacting with, none of which is appropriate for a claim to composition of matter as we have here.

29. In my opinion, the '523 patent is clear that this term means a group of atoms which includes at least one reactive carbon atom capable of forming a bond with X. Although the '523 patent provides a list of ***examples*** of residues comprising activated carbon atoms that

includes carbons at various positions in aromatic compounds (Ex. 1 at 6:39-48), nothing in the specification limits the claims to these examples as Roche contends. Thus, a POSA would understand this term to carry a meaning that accords with the plain language of the claim.

3. "E"

30. In my opinion, the meaning of the term "E" in the '523 patent means exactly what claim 1 states: E is "O, NH or an acyclic divalent sulfur atom." (Ex. 1 at 38:44.) All three of these chemical groups were well-known and their meaning readily understood by a POSA at the time of the invention.

31. Nothing else in the '523 patent or file history contradicts this reading of the plain language of the claim or requires the added method step that E "underwent a reaction to form a bond" as Roche's construction seeks to import. The proposed addition of this method step to a composition of matter claim is inappropriate.

4. a. "comprising…"

b. "…biotin…"

c. … chelator or a compound capable of yielding a metal chelator"

32. I understand that the parties dispute the meaning of this phrase as a whole as well as several of the terms within it. I will address each issue in turn.

33. In my opinion, the claim phrase as whole does not require construction, because its meaning is clear from the '523 patent.

a. comprising

34. In the context of the '523 patent, a POSA would understand the claim term "comprising" to be open-ended in that it allows for atoms in addition to those specified in the claim. While this should include any atoms used to link the specified molecules to E, it should

not be limited to only those additional atoms as Roche contends. (*See*, *e.g.*, Ex. 1 at 14:50-52; 12:19-20:5.)

b. biotin

35. With respect to the term "biotin," I disagree that this term should be limited to the specific structure proposed by Roche. In my opinion, the plain meaning of the claims and disclosures of the '523 patent, support a broader scope of this term that includes any biotin derivatives, analogues and moieties which may be used "wherever biotin/avidin or biotin/streptavidin-based pairs or detection systems have been used in the prior art." (Ex. 1 at 5:1-12; *see also*, *e.g.*, 7:61-62; Table 1; 17-18 (Scheme VI); claim 37.) Notably, the '523 patent does not provide a specific chemical structure for biotin. Rather, it explains that the claimed detectable molecules may contain a broad class of "biotin moieties." In fact, the biotin moieties depicted in the '523 patent contain more atoms than that of the structure proposed by Roche, so Roche's proposed construction cannot be correct. (Ex. 1 at Table 1; claim 37.)

c. chelator or a compound capable of yielding a metal chelator

36. In my opinion, a POSA would understand that the meaning of the plain language of the claim phrase "chelator or a compound capable of yielding a chelator" to be a chemical compound or agent that can complex or combine with a metal ion to become part of a chelate. The word "chelator" comes from the Greek word for claw. Therefore, a chelator/claw is a compound that can grasp and bind a metal to become part of a complex called a chelate. Other claims in the patent, such as claim 2, confirm and illustrate this plain meaning of a chelator being part of a chelate by providing a chemical structure for Det^{b}, a chelator that is complexed with "M," a "radiometal."

37. A POSA would also readily understand this plain meaning from numerous other disclosures in the '523 patent. (Ex. 1 Abstract; 1:15-20; 3:48-65; 4:34-47; 7:61-8:39; 8:40-9:9;

20:54-65; 21:20-25; 33:21-34:58; claims 1, 2, 15, 27, 32, 33, 34, 36, 40; 1:44-45 (citing relevant Sundberg article (Ex. 7)); 1:67-68 (citing relevant Scheinberg article (Ex. 8)); and generally 12:19-20:5 (Methods). Nothing in the '523 file history contradicts this plain meaning.

38. Finally, I note that the testimony of Roche's witnesses and the literature that I have reviewed further support my conclusion as to the meaning of this claim phrase. (Exs. 11, 12, 14.)

5. "said complex"

39. I disagree with Roche's position that this claim term is indefinite. In my opinion, the term "said complex" means and refers to the said composition, comprising the detectable molecule which binds or complexes with the claimed analyte. That meaning would be clear to a POSA from reading the plain language of claim 15 which is directed to a method of using the novel detectable molecule of claim 1 to check for the presence or absence of a desired compound, i.e., an "analyte," in a test sample. For example, I might check a blood sample to see if a patient has hormones normally present when pregnant. According to claim 15, the first step of the method is to contact the test sample with "a composition which comprises . . . the detectable molecule of claim 1," plus other ingredients such as buffers. In my experience, in order to observe the amount of detectable complex that forms between the detectable molecule of claim 1 and an analyte in the test sample, one would have to "separate any complex formed between the analyte" and the detectable molecule in the composition. Thus, it would have been clear to a POSA that "said complex" as that term appears in subsection (b) of claim 15 must mean and refer to the said composition in element (a) of the claim which comprises a detectable molecule.

40. The '523 patent claims and specification fully support this reading. Claim 2 element (b) directed to a specific binding assay method, and has language corresponding to claim

15, and also claims a step of separating any complex formed between the detectable molecule in the composition and the analyte. Further, the patent states that the invention may be used in all manner of applications including sandwich and competitive assays, and hybridization assays. (Ex. 1 at 20:8-23.) A POSA would have understood that these assays typically include a step in which analyte bound in a complex with the detectable molecule would be separated from the rest of the original composition ingredients.

VI. OPINION CONCERNING THE '830 PATENT

A. Background

41. The '830 patent issued on January 21, 1992 from Application No. 160,607 filed on February 26, 1988, and expired on January 21, 2009. (Ex. 2.)

42. The '830 patent is directed to oligonucleotides and polynucleotides (i.e., nucleic acids) that have at least one label which is involved in the process of generating a signal, attached at or near each of the 5' and 3' ends of the oligonucleotide or polynucleotide. The '830 patent refers to these labels as "non-radioactive moieties" and discloses that they include a variety of molecules such as the vitamin biotin and its analogues, enzymes, fluorochromes, or chromogen. (Ex. 2 at 1:21-27; 3:41-46.) According to the Federal Circuit, so long as the label is capable of detection with a preformed detectable molecular complex[3], it qualifies as a "non-radioactive moiety." (*See* ¶ 13 above.)

43. A particularly novel aspect of the '830 patent is that the non-radioactive moieties are added in positions where (1) the ability of the non-radioactive moiety to be involved in the signaling process is not hindered; (2) the stability of the oligonucleotide or polynucleotide is preserved; and (3) the ability of the oligonucleotide or polynucleotide to hybridize with a

[3] The '830 patent provides an example of a molecule comprising avidin or streptavidin and a biotinylated enzyme as a "preformed detectable molecular complex." ('830 patent at 3:46-53.)

corresponding nucleic acid sequence remains intact. (Ex. 2 at Examples 1-3.) With such a novel molecule, it is possible to perform tests on a wide variety of biological (e.g., serum, plasma, urine, etc.), physiological (e.g., buffers, preservatives, antimicrobial solutions), industrial, environmental, and other sample fluids, in order to determine whether, for example, a specific substance is present. (Ex. 2 at 2:48-3:3.)

B. Person of Ordinary Skill in the Art

44. It is my opinion based on the materials I have reviewed and my own knowledge of the state of the art during the relevant time frame of the '830 patent, that a POSA at the time of '830 invention would have been person in the field of chemistry who possesses or could have been actively pursuing an advanced degree in chemistry (i.e., Masters or above) and who has done course work in life sciences (e.g., molecular biology, biochemistry).

D. Claim Construction of Disputed Claim Terms

1. "oligo- or polynucleotide"

45. After reviewing the '830 patent and file history, I conclude that a POSA would understand the term "oligo- or polynucleotide" to mean "a chain of three or more nucleotides directly linked to each other in an uninterrupted continuous sequence." In a section entitled, "Oligonucleotide Synthesis," the '830 patent discloses a synthesis of oligonucleotides by the phosphoramidite method. (Ex. 2 at 6:23-42.) In this method, which would have been known by a POSA at the time, single nucleotides (such as that in Figure 1) are covalently linked to each other one by one. The first two nucleotides attach together to form a dinucleotide. (Ex. 19.) The addition of more nucleotides to that dinucleotide leads to the synthesis of an oligonucleotide made up of a continuous sequence of nucleotides. (*Id.*) Oligonucleotides synthesized by this method are shown in Table 1 of the '830 patent. (*Id.*; Table 1.) Notably, they only contain

sequences of nucleotides or modified nucleotides, and are not interrupted by any non-nucleotide moieties.

46. I disagree with Roche's proposed construction at least insofar as it imports a requirement into the claim that all of the nucleotides in the claimed oligonucleotides and polynucleotides except those at the 5' and 3' ends be naturally-occurring. I do not find any ambiguity in the term "oligo- or polynucleotide," as it has a well-accepted plain and ordinary meaning to those of ordinary skill in the art. Further, I have reviewed the specification of the '830 patent and find no disclosure whatsoever that suggests to a POSA that the inventors sought to impart a special definition to the phrase, nor does the file history suggest that the inventors limited the scope to "naturally-occurring" nucleotides. Moreover, the '830 patent directly contradicts Roche's construction because it discloses oligonucleotides that contain nucleotides at positions other than the 5' and 3' ends, which have been twice modified with a linker group and then a biotin. ('830 patent at Figure 1; 3:63-4:1; 4:57-6:22.) Roche's proposed construction also contradicts what a POSA would have understood the broad term nucleotide to mean at the time – a moiety comprised of a phosphate group, a sugar, and a base. In fact, I note that Roche itself refers to continuous sequences of non-naturally-occurring nucleotides called "locked nucleic acids" (LNA) as "oligonucleotides." (Ex. 15 at, e.g., RE001030141.) Roche's use of the term "oligonucleotide" with respect to LNAs is consistent with the plain and ordinary meaning and shows that those of skill in the art refer to nucleic acids containing non-naturally occurring nucleotides as "oligonucleotides."

47. I also disagree with Roche's construction because it improperly injects an intended *use*, i.e., as a probe, into a claim to a composition of matter. This is a deviation from the clear understanding a POSA would have as to the broad term "oligo- or polynucleotide." Though the '830 patent does discuss the capacity of an oligonucleotide or polynucleotide to hybridize to

complementary sequence and the possibility of its use as a probe, the '830 patent states that its novel invention is not so limited. (Ex. 2 at 3:9-16.) Claim 1 does not contain the word "probe." This is in contrast with independent claim 18 claiming a *method* which expressly requires "an oligo- or polynucleotide probe." (Ex. 2 at 14:58-59.) If "oligo- or polynucleotide" simply meant "probe" as Roche incorrectly concludes, there would be no reason to specify that particular use in claim 18. Further, the '830 patent discloses other uses for the claimed oligonucleotides and polynucleotides including to measure the capacity of a specific moiety to bind a compound. (Ex. 2 at 2:66-3:8.)

48. I also note that since the patent explains that the *entire* claimed invention (including at least one non-radioactive moiety at each end) may be used as a probe, within the context of the patent, the hybridizing oligonucleotide or polynucleotide portion of the whole claimed molecule does not by itself have a probe-use within the context of the '830 patent.

2. "having"

49. I am informed that Roche wants the Court to construe this term to mean "consisting of," and that Roche argues the claims exclude additional elements not specified in the claim. Roche's position is unsupported by the '830 patent. In my opinion, the claims allow for elements in addition to those specified in the claim.

50. The '830 patent explains that the non-radioactive moieties (e.g., biotins) at or near each of the 5' and 3' ends of the oligonucleotide or polynucleotide may themselves "further serve to attach a biotinylated polymer." (Ex. 2 at Abstract; 2:18-25.) Claim 10 further explains that such polymer may be attached to a biotinylated polymer. That polymer may be dextran, which is a complex molecule made up of multiple branches of glucose molecules. (Ex. 2 at Claim 10.) Thus, the patent discloses an invention in which additional elements beyond the non-radioactive moiety may be present.

51. I am informed that Roche's position is that "having" means "consisting of." This is not consistent with the claims and context of the '830 patent. That construction would literally require that the claimed oligonucleotide or polynucleotide "consist of" non-radioactive moieties, i.e., non-nucleotides, and terminal nucleotides (as opposed to having the non-radioactive moieties attached to an oligonucleotide or polynucleotide as stated in the claim). For the reasons stated above, that result is inconsistent with what a POSA would understand the term "oligonucleotide or polynucleotide" to mean, i.e., a chain of three or more nucleotides directly linked to each other in an uninterrupted continuous sequence. Further, there is nothing within the specification that suggests the inventors intended to exclude additional structures or atoms from the claims.

3. a."at least one non-radioactive moiety . . . attached to each of the 5' and 3' end nucleotides"/"at least one non-radioactive moiety . . . attached to each of the 5' and 3' terminal nucleotides"

52. I disagree with Roche's construction of these terms for at least the reason that it improperly imports aspects of a process and results, i.e., "to enhance the signal generating output," into a claim to a composition of matter. A POSA would understand that the plain language of the claims does not include this requirement. As I explained above, the '830 invention is novel because, as the '830 patent discloses and teaches, the non-radioactive moieties are attached at the 5' and 3' ends of the oligonucleotide or polynucleotide without impeding their involvement in a signaling process or otherwise interfering with the hybridization process and, with increased stability. (Ex. 2 at 10:33-43; 11:68-12:3; Fig. 3.) This fact is confirmed by the '830 patent file history. (Ex. 5.) Thus, even setting aside the fact that no processes/results would or should be included within the meaning of this claim term, Roche's construction is unduly limited to only one of the exemplary processes and results discussed in the '830 patent.

Furthermore, to a POSA, the claim describes well-defined structures and Roche's proposed functional language does nothing to further clarify those structures.

4. "at least one non-radioactive moiety directly or indirectly attached to each of the 5' and 3' terminal nucleotides external to a target hybridization region"

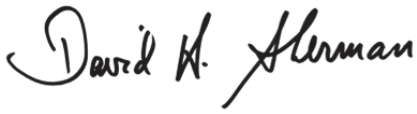
53. In my opinion, this term means that the non-radioactive moieties attached to each of the 5' and 3' terminal nucleotides must be external to a target hybridization sequence of the oligonucleotide or polynucleotide. To be clear, this means that the 5' and 3' end nucleotides to which the non-radioactive moieties are attached may themselves be part of the target hybridization sequence. The non-radioactive moieties define and are external to a target hybridization sequence comprised only of nucleotides that is capable of hybridizing a complementary sequence, with those non-radioactive moieties being attached to the 5' and 3' termini thereof. This meaning would be clear to a POSA from the '830 patent claims and of the specification.

54. The '830 patent is clear that any group extending from either of the 5' and 3' termini such as non-radioactive moieties, "tails" or "terminal extensions" including groups containing nucleotides (e.g., oligomers 9, 13, and 15 of Table 1), is not "internal" (like oligomer 10, Table 1, 9:41-42 and 11:19-21) but described as "external" or "outside the hybridizing sequence." (Ex. 2 at 13, and Tables 1-3.) The exemplary target hybridization sequence in the '830 patent as depicted in Table 1, is a continuous, uninterrupted chain of nucleotides that is complementary to the bases in part of the *E. coli* lac gene of bacteriophage M13 mp series DNA, i.e., the 17 base sequence GTCATAGCTGTTTCCTG. (Ex. 2 at 8:62-65; Table 1.) Oligomers 9, 13 and 15, for example, have non-radioactive moieties that are external to this target hybridization sequence. (Ex. 2 at Table 1; see also Table 3.) The '830 patent is clear that the non-radioactive moieties, i.e., biotin labels, on oligomers 9, 13, and 15, are "outside the hybridizing

sequence" extending from the 5' and 3' termini and that this is an effective site for the introduction of biotin. (Ex. 2 at 13: 16-19; Table 3.) Thus, persons of skill in the art would understand from the '830 claims and specification that this claim term refers to non-radioactive moieties that are attached to and extend from the 5' and 3' terminal nucleotides of a target hybridization sequence of the claimed oligo- or polynucleotide. Based on this clear guidance, it would be understood that any group external to the 5' and 3' phosphates of the oligomer are, by definition, external to the hybridization sequence of the oligomer.

55. Roche's proposed construction is at odds with the teaching of the '830 patent which discloses that attachment of labels will not interfere with the ability of the label to be involved in the signaling process, or the stability or capability of an oligonucleotide or polynucleotide to hybridize so long as the labels are positioned at or near the ends of the sequence.

I declare under penalty of perjury that the foregoing is true and correct.



Dated: December 20, 2013

By: _____
David H. Sherman, Ph.D